REMARKS

Status of the Claims

Upon entry of the instant amendment, claims 94-96 and 98-119 are pending in the above-identified application and stand ready for further action on the merits. Claims 96, 101 and 106-116 are withdrawn from consideration as being drawn to non-elected inventions and species.

New claims 118 and 119 have been added, and are at least supported at pages 10-13 of the Specification. Accordingly, the present amendments to the claims do not introduce new matter into the application as originally filed.

As such, entry of the instant amendment and favorable action on the merits is earnestly solicited at present.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 94, 95, 98-100, 102-105 and 117 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse.

In the Office Action it is alleged that the Specification, while being enabling for making those glycoconjugates having a well-known utility, "does not reasonably provide enablement for the scope of the glycoconjugates made by said method." It is further asserted that "[a]bsent a well-known, or specific and substantial utility, one of skill in the art would not know how to use the products made by the scope of the instant method." Applicants respectfully disagree.

The claimed methods do not yield just a single, specific compound or molecule. (In fact, if the claimed methods were directed to producing only a single molecule, they would be of very little utility.) Instead, the utility of the claimed methods resides in their production of complex oligosaccharide mixtures. That is, the mixtures themselves have specific, substantial and individual utility, in that they provide combinations of individual compounds/molecules. The mixtures can be used as markers for authentication, molecular libraries, or in foods, among others.

Complex mixtures prepared by the claimed methods can have undeniable specific and individual utility as product marking compositions, because of the very nature of the mixtures. It is not necessary to establish the utility of each individual molecule, to establish the utility of a mixture of the molecules as a whole, as is demonstrated by the complex saccharide profiles described in the Examples and Figures 12 and 13.

Figure 12 is a mass profile of a mixture of products produced using the claimed invention, wherein the monosaccharides fucose, galactose, and N-acetylglucosamine are reacted. The mixture includes molecules with all three monosaccharide residues, and the molecules include different residues and molecular weights. Similarly, Figure 13 is a mass profile of a mixture of products produced from four different sizes of monosaccharides (xylose, fucose, galactose, and N-acetylglucosamine). It would be readily apparent to one of skill in the art that the mass (molecular weight) fingerprint defines a unique composition (mixture of compounds), that would be difficult to duplicate and identify through routine experimentation.

The concept of marking products (using a carbohydrate profile/fingerprint of a mixture prepared by the claimed methods) is discussed in the Specification at least at page 36, line 36 to page 37, line 13 and page 85, line 5 to page 86, line 6. The Specification teaches that these fingerprints (based on the molecular mass of the molecules in the mixture) cannot be reproduced without prior knowledge of the original raw materials and reaction conditions. Thus, for example, a compound mixture produced by the claimed invention having a specific mass profile could be associated with a sealed container containing a valuable food or drink (page 37, lines 2-6). The food or drink could then be authenticated using the carbohydrate mixture by examining its mass profile, much like hologram tags are used to authenticate banknotes, among others. The methods described on page 37 of the Specification include adding (a) a carbohydrate which can be recognized by a specific enzyme (such as a reporter), (b) a binding molecule, or (c) an isotopic label to a mixture produced by the claimed invention. One skilled in the art would recognize that such mixtures of compounds would be impossible to copy without authorization.

Furthermore, it would be obvious to one of skill in the art that the mixtures of compounds produced by the claimed invention have utility as molecular libraries for screening bioactive molecules. As pointed out by the Examiner, mixtures of glycoconjugates produced by the

claimed methods can be used as carbohydrate/saccharide libraries. Such libraries are valuable research tools, and depending on the nature of the screening/selection of a library, some of carbohydrates/saccharides present may be found to have activity, while others do not. Thus, while one compound in the library may have activity, when screening the library under a first set of conditions, the same compound may not be active, when the library is screened under a second set of conditions. However, the library (mixture of compounds) as a whole has utility under both sets of conditions, even if only to indicate that there is no activity with a library prepared using specific saccharides as reactants.

The claimed invention can be used to produce a library of compounds, which can be screened for biological activity, as suggested by the references cited by the Examiner. The utility of the library exists because its screening produces positive or negative signals, not because a specific bioactive molecule is present. There is specific utility in providing information about the interaction of the mixtures produced by the claimed invention and a biological agent. If screening of the library is negative, the utility is in the knowledge that the biological activity sought does not exist with regard to the library being screened. Such information derived from screening of a library prepared using the claimed invention would be useful to one of skill in the art.

In the Office Action it is alleged that the products of the claimed invention do not have a GRAS status. With regard to food products, the GRAS status for specific materials would be obvious to one of skill in the art in the context of nutraceutical carbohydrates based on examples previously given.

In the Office Action there are statements specifically referring to glucuronic acid in alginate potentially triggering unwanted effects such as antibody generation, and bacterial exopolysaccharides possibly stimulating an undesired immune response. These statements may be referring to data about injected carbohydrates, as one of skill in the art would know that alginate is a GRAS product very widely used in the food industry. Applicants are unaware of reports of harmful effects due to the ingestion of carbohydrate materials that fall within the scope of the claimed invention. Applicants respectfully request that the Examiner provide specific citations supporting the allegation that carbohydrates falling within the scope of the claimed

invention are unsafe for human consumption. One of skill in the art would know that the vaccine effects that occur *in vivo* after injection of a material into a tissue are not relevant to the activity of the molecules in the gastrointestinal-tract (practically all GRAS foods would be lethal if injected into a body). It is asserted in the Office Action that GRAS status does not provide utility. However the major use of polydextrose products (as disclosed by the references cited by the Examiner) is in their reduction of biodegradation and their fiber-like function, and one of skill in the art would recognize that this is applicable to the products of the claimed invention.

In the Office Action it is alleged that the scope of the claims is infinite and any possible chemical structure could potentially be used as the glycoconjugate made by the claimed method. Applicants respectfully disagree. The Specification and claims recite specific carbohydrates used in the claimed invention and the nature of the raw materials (reactants) limit the composition of the product mixtures. One skilled in the art would recognize that not all carbohydrates would react according to the claimed invention, let alone just any molecule.

One of skill in the art would find that the claimed invention provides synthesis methods that would inevitably produce a multitude of possible products. The statements made in the Office Action appear to imply that the claimed methods would only be patentable if they resulted in the production of a single specific molecular product.

Claim 95 further defines the reaction substrates and claim 100 defines the product as oligosaccharide products within a defined range of sizes. Claim 105 also specifically defines how monosaccharide residues in the product are linked together.

New claim 118 further defines the product of the claimed methods as comprising products with different substrate carbohydrates or monosaccharide residues thereof glycosidically linked to each other, and new claim 119 further defines the product of claim 118 as comprising homotypic glycosidically linked oligomers or polymers of several substrate carbohydrates. These new claims are at least supported by the Specification at pages 10-13.

In view of the discussion above, Applicants respectfully request that the rejection of claims 94, 95, 98-100, 102-105 and 117 under 35 U.S.C. § 112, first paragraph, be withdrawn.

CAM/SAW/kml

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

Claim 102 is rejected under 35 U.S.C. § 1112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention. Specifically, it is stated in the Office Action that the phrases "bitter taste" and "undesired color" are relative terms rendering the claim indefinite. Applicants respectfully traverse. The bitter taste and undesired color are inherent properties of the levoglucosan recited in claim 102.

In support of the assertion that "bitter taste" is a relative term, it is stated in the Office Action that there is genetic variation in the ability to taste a bitter substance. One of skill in the art would be aware that any biologic activity is subject to individual variations and that the activity must be considered on average within a given population. The argument concerning genetic variability would seem to make almost any pharmaceutical unpatentable.

In the Office Action it is stated that "Rennhard improves the process so as to not impart unnatural colorations to the product (Rennhard column 3, lines 40-45). As defined by Applicants, the formation of anhydro products causes the undesired color in the product." The discolorant disclosed by Rennhard is associated with polymers. (*See* Rennhard at column 4, lines 74-75.) Rennhard does not teach soluble levoglucosan, as in the claimed invention. Applicants respectfully point out that the claimed invention is directed to a different process of condensing different carbohydrates to react with each other than taught by Rennhard. Which side-products are formed in the Rennhard processes, especially the Rennhard processes using high amounts of polycarboxylic acids, cannot be known.

In view of the discussion above, Applicants respectfully request that the rejection of claim 102 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 94, 95, 98-100, 102-105 and 117 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kanie et al., "Solid Support Oligosaccharide Synthesis and Combinatorial

Carbohydrate Libraries, 2001, pp. 239-256 (hereinafter "Kanie") in view of Rennhard, U.S. Patent No. 3,766,165 (hereinafter "Rennhard"), and in further view of Tibor Mora et al., U.S. Patent No. 2,719,179 (hereinafter "Tibor Mora"). Applicants respectfully traverse.

It is stated in the Office Action that "[a]n activating group at the C1 position [as disclosed by Kanie] does not transform the reactive C1 position into a group that does not react under conditions where the non-transformed group reacts, therefore an activating group is not a protecting group and a saccharide bearing a C1 activating group is non-protected at the C1 position." The function of the group at the C1 position is to increase the anomer specific reactivity of the donor. It is an additional activating structure which is not part of a) the claimed invention or b) the teachings of Tibor Mora and Rennhard. Referring to Figure 12.6, it is stated in the Office Action that the acceptor molecule is not protected ("coupling to an acceptor molecule that does not carry any protecting groups"); however the anomeric carbon of the acceptor B is protected by a group R which is stable during the deprotection steps. The same is shown in Figures 12.7, 12.12 and 12.13. Furthermore, as noted by the Examiner, the C1 position contains an activation group and the monosaccharide derivative is protected by a benzyl group to each hydroxyl group position other than C1. (*See* Figure 12.6, where B is the donor, PO is a protecting group, and L is an activating or leaving group. The same is shown in Figures 12.7, 12.12 and 12.13.) Thus, the statements made in the Office Action are contradictory, as it is first asserted that the C1 group of the donor is not a protecting group, immediately followed by an admission that the donor is protected. One of skill in the art would know that the raw materials disclosed by Kanie and the non-activated/non-protected materials of Tibor/Rennhard are clearly different from each other, and one of skill in the art would therefore not combine the teachings of Kanie and Tibor/Rennhard, as their teachings are directed toward completely different chemistries.

The protection strategy taught by Kanie leads to completely different reaction products than those taught by Tibor Mora/Rennhard. One of skill in the art would appreciate the methods disclosed by Kanie could not be used to produce the product taught by Tibor Mora/Rennhard, if it was applied to the monosaccharides taught by Tibor Mora/Rennhard, simply because the Kanie acceptor molecule is always C1 protected. In the Kanie method, (a) the donor molecule cannot

react with itself or (b) the acceptor molecule cannot react with another acceptor or with the donor at C1.

The Kanie products are derivatives of an acceptor saccharide modified by a donor saccharide. In contrast, the present reactions provide products from reactions of C1 anomeric positions of both saccharide 1 and saccharide 2 and vice versa, as well as each of saccharides 1 and 2 with themselves.

Furthermore, Kanie does not disclose polysaccharides and Tibor Mora/Rennhard do not disclose oligosaccharides. Based on IUPAC definitions, the products of Kanie are not polysaccharides but oligosaccharides (by definition DP<10), while Rennhard and Tibor/Mora products are defined as polysaccharides and produced by polymerization processes. In particular the first paragraph of Tibor Mora and the second column, second paragraph, second sentence indicate a minimum Mw of 2500 (more than 15 monosaccharides) and sizes up to a Mw of 1 000 000. Rennhard consistently teaches a polymer product (*see*, *e.g.*, the end of third column at the beginning of the description). The minimum average molecular weight of Rennhard is about 1500, which one of skill in the art would expect with polymer products (end of column 6 and Examples even disclose much larger products). Kanie, on the other hand, is consistently directed to oligosaccharides (the title on the first page; page 240, line 4; the title of paragraph 12.2; page 242, first line of paragraph 12.2.2.; title of paragraphs 12.6, 12.7 and 12.8 at pages 250, 252, and the first two lines of conclusions on page 254, respectively, and the examples discussing only trisaccharides or trisaccharide mixtures).

The term "polysaccharide" appears to be applied to all the cited references in the Office Action. Applicants respectfully disagree with this characterization of the teachings of the cited references. Furthermore, the product taught by Kanie is fundamentally different from the claimed product. In order to arrive at the claimed invention, one of skill in the art would be required to know specifically which conditions to select from those disclosed by the cited art and they would not be those taught by Kanie, where only one monosaccharide is added to a specific C1 protected monosaccharide.

As stated in the Office Action, Tibor Mora discloses processes using monosaccharides and tetrasaccharides as starting materials, such as "glucose, xylose, acetylated glucose and 2-deoxy amino glucose (column 3, lines 15-30)." This teaches away from the present invention.

Aside from the simplest aldo pentose and hexose molecules, the Examiner also notes the teaching of acetylated glucose and 2-deoxy amino glucose by Tibor Mora. The latter two saccharides do not fall within the scope of the claims. Further, when the teachings of Tibor Mora and Kanie are combined, they do not lead to the same products as those produced by the claimed invention, because, as one skilled in the art would know, the acetyl group in acetylated glucose acts as a protecting group (the cited paragraph refers to other protecting groups, such as benzyl methyls, among others), and hexosamines of 2-deoxy amino glucose are inactive in reactions of the claimed invention. Based on the cited publications, these monosaccharides would be among the first to try, and they would not lead to the claimed invention. Thus, their combination in effect constitutes a teaching away from the claimed invention.

The claimed invention provides new reactions under special condensation conditions between a limited group of carbohydrates which have not previously been shown to react with each other and the invention excludes non-reactive molecules (*e.g.*, GlcN or GalN as taught by Tibor Mora).

Rennhard does not teach the claimed reactions, but rather teaches simple glucose polymerizations. Rennhard is specifically directed to polycarboxylic acids which are used to ester cross-link carbohydrates to create highly polymeric molecules (column 4, paragraph 4). This feature is required by Rennhard's claims and it further makes the Rennhard product very different from those taught by Kanie or Tibor Mora.

The teachings of Kanie are directed to traditional organic chemistry reactions of an activated and protected donor with a partially unprotected acceptor. Furthermore, the methods taught by Kanie appear to work only with a specific leaving group disclosed by Kanie or two other groups referenced. Such reactions are performed in organic solvents and are often carried out at temperatures below 0 degrees Celsius. The reactions taught by Tibor/Rennhard are directed to condensation reactions of simple sugars.

Kanie does not teach condensing polysaccharides, as in the claimed invention. It is asserted in the Office Action that "[a]ll of Kanie et al., Rennhard, and Tibor Mora et al. are drawn to the field of condensing polysaccharides." Applicants respectfully disagree. This is an extreme oversimplification of the art and does not follow from the teachings of the cited art. The level of organic chemistry related to the teaching of Kanie is a complicated art. The reactions do not involve condensation of monosaccharides, but involve at least one specifically protected (non-anomeric) position, a C1-activated monosaccharide residue derivative, and another monosaccharide C1 protected acceptor saccharide. The allegation that Kanie teaches a simple polysaccharide condensation reaction is refuted by Kanie's multi-step protection and deprotection reactions scheme and the protecting and activating group strategies taught by Kanie. Furthermore, one of skill in the art would acknowledge that use of the term "polysaccharide" is inaccurate when referring to the teachings of Kanie.

Kanie teaches that the multiple hydroxyl groups of saccharides are responsible for the multifunctionality and complexity of oligosaccharide synthesis (page 239, introductory paragraph 12.1). Such a generalization does not provide sufficient detail to form the basis of a rejection, although the second to last sentence of the introductory paragraph is relied on in the Office Action. The very next sentence (last sentence of the introductory paragraph) explicitly states that a protecting group (as is required by Kanie in the donor and C1 of the acceptor) are absolutely needed, where it states, "Therefore in order to control stereo- and regiospecificity, orthogonal protecting group manipulations and the introduction of special protecting groups at the C2 position are necessary.

Kanie teaches production of specific oligosaccharides using specific conditions and with reagents that permit glycosidic linkages to be formed between specific monosaccharide residues. However, it would immediately be obvious to a skilled artisan that Kanie's teachings are not relevant to the condensation chemistry used to synthesize the completely different polysaccharide products of the claimed invention.

It is alleged in the Office Action that "[i]t is well within the level of ordinary skill in the art to combine the reaction conditions within the field of condensing polysaccharides through routine experimentation." The argument in the Office Action appears to be that because specific

oligosaccharides can be made using the teachings of Kanie, any other carbohydrate products (including carbohydrates that are clearly different from the products taught by Kanie) would be obvious to make by any possible method (such as the polysaccharide condensation chemistry taught by Tibor/Rennhard). If this were the case, there would be nothing left to be patented in the field of chemistry, and nothing should have been patentable in the field of chemistry for decades.

Applicants respectfully suggest that the Examiner may be using information from the present application to alter the technical content of the Kanie reference, in order to combine Kanie's teachings with those of the other cited publications. By doing so, it alters the scope of the products produced by the cited references such that they turn out to be the same as the products of the claimed methods.

Kanie teaches reactions of traditional protected and activated monosaccharides with non-protected acceptors in polar organic solvents and the production of oligomers of various monosaccharide types. Kanie provides no evidence that similar reactions would occur if (a) the donor monosaccharides are not activated; (b) the donor monosaccharide is not protected, or more specifically not protected by benzyl groups (it is known in the art that other protection strategies affect the donor reactivity with the activated monosaccharides); and (c) acid or heat catalysis is used in a dry or aqueous environment.

The monosaccharide types taught by Tibor Mora and Rennhard are not reactive (with each other or otherwise) using the conditions taught by Kanie.

The proposed combination of references does not take into account the problems associated with combining the different reaction conditions and substrates and then, selecting from all the possible combinations of the teachings of Kanie, Rennhard and Tibor Mora to arrive at the precise conditions that would result in the claimed invention. The Kanie reaction falls within the field of regular organic chemistry and cannot be relied upon for predicting the outcome of the reactions of non-protected saccharides using conditions taught by Rennhard and Tibor Mora. Similarly, the reaction conditions and reagents taught by Rennhard and Tibor Mora do not include the claimed monosaccharide types and cannot be relied upon to predict the

success of the reaction conditions, if applied to the molecules taught by Kanie or their non-protected variants.

There are at least 6 possible ways to combine the teachings of the cited prior art, and they are as follows:

1) Rennhard/Tibor Mora reaction conditions, Rennhard/Tibor Mora solvent/dry feature and Kanie molecules with activation and protection;

2) Rennhard/Tibor Mora reaction conditions, Kanie solvent feature and Kanie molecules with activation and protection;

3) Rennhard/Tibor Mora reaction conditions, Kanie solvent feature and Rennhard/Tibor Mora substrates;

4) Kanie reaction conditions, Kanie solvent feature and Rennhard/Tibor Mora substrates;

5) Kanie reaction conditions, Rennhard/Tibor Mora solvent/dry feature and Kanie molecules with activation and protection; and

6) Kanie reaction conditions, Rennhard/Tibor Mora solvent/dry feature and Rennhard/Tibor Mora substrates.

It is obvious in hindsight that many of the combinations would likely result in catastrophic failures (and not the claimed invention), and there would be no obvious reason for one of skill in the art to try some combinations over others.

Ignoring the possible combinations listed above, the Examiner claims that it would have been obvious to one of skill in the art at the time the invention was made to combine:

7) Rennhard/Tibor Mora reaction conditions, Rennhard/Tibor Mora solvent/dry feature, and Kanie substrates modified to non-protected and non-activated form as taught by Rennhard/Tibor Mora, to produce the products of the claimed methods (rather than using single monosaccharide additions in each step as taught by Kanie or derivatives of single simple sugar types taught by Rennhard/Tibor Mora).

Beginning with the reactions taught by Tibor Mora, there are three parameters (reaction conditions, solvent and substrates) and there are four possibilities (Kanie, Rennhard/Tibor Mora,

Kanie modified to Rennhard/Tibor Mora and Rennhard/Tibor Mora modified to Kanie) for each of the three parameters, which means that there are 64 alternative combinations (4 x 4 x 4) minus the two original conditions (Kanie or Rennhard/Tibor Mora), so that there are 62 variations from which the Examiner selected the combination which might lead to the claimed invention. Such a selection can only be made based on hindsight and knowledge of the claimed invention. Considering just the Kanie protection or activation feature or the differences between Rennhard and Tibor Mora, the actual number of reaction possibilities that one of skill in the art would have to choose from would actually be extremely large. Most of these combinations would appear to be useless, and in screening efforts, using all possible carbohydrates or carbohydrate reactable molecules (there are also conjugates in Kanie), the number of possible combinations would be endless without a realistic expectation of finding a specific useful compound.

Furthermore, the expectation of successfully making the products produced by the claimed methods would be very low using the conditions disclosed by the cited art or using modified conditions by combining the teachings of the cited art. One skilled in the art would have no reason to expect any special success without first having knowledge of the claimed invention.

In summary, the disclosure of Kanie is totally different from the claimed invention and from the disclosures of Tibor Mora and Rennhard with regard to (a) the raw materials; (b) the products; and (c) the reactions.

Therefore, Applicants find that one of skill in the art would not be motivated to combine the teachings of the cited art as suggested in the Office Action with reasonable expectation of success, and that a detailed analysis of the art and cited references shows that such a combination of the teachings is not reasonable without employing hindsight.

To arrive at the claimed invention, combination of the teachings of the cited art would require altering the raw materials, reactions and products with regard to Kanie, and raw material and products with regard to Tibor Mora/Rennhard, and this can only be done by using hindsight based on the claimed invention.

All of the features of the claims should be disclosed in the cited art, but the teachings of the cited art cannot be combined as suggested by the Examiner without violating the teachings of the cited art itself or using improper hindsight.

In view of the discussion above, Applicants respectfully request that the rejection of claims 94, 95, 98-100, 102-105 and 117 under 35 U.S.C. § 103(a) as being unpatentable over Kanie in view of Rennhard and in further view of Tibor Mora be withdrawn.

CONCLUSION

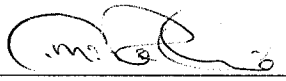
In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Stephanie A. Wardwell, Reg. No. 48,025 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Dated: DEC 30 2009

Respectfully submitted,

By 

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